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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
02/03/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/027,205	JUNE ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *96,97 and 99-107* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *96, 97,99-197* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/07/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/07/2010 has been entered.

Claims 96-97 and 99-107 are pending in the instant application

Claims 1-95 and 98 have been canceled previously.

2. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 96-97 and 99-107 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over June et al. (WO 95/33823) in view of Chang et al. (U.S. Patent No. 6,129,916) (of record), Levine et al. (International Immunology 7: 891-904, 1995) (1449; #CI), Kwon et al. (U.S. Patent No. 5,569,997) (of record) and Allaway et al. (US 2004/0086528 A1) (of record) for the reasons of record.

Applicant's arguments, filed 01/07/2010, have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant argues the following.

Applicants contend that June et al. teaches the proliferation of T cells by contacting the T cells with anti-CD3 and anti-CD28 antibodies immobilized on a microbead. Chang et al. and Levine et al. teach beads comprising multiple antibody specificities, including anti-CD3 antibodies and anti-CD28 antibodies. However, June et al. in view of Levine and Chang fail to address the effect of contacting T cells with bead immobilized anti-CD3 and anti-CD28 antibodies on CCR5 expression. The Examiner pointed to Kwon (particularly first paragraph, Col. 28) and found Kwon et al. teach that the ligation of T cells with anti-CD3 antibodies and anti-CD28 antibodies induce an HIV virus resistant state, which appears to be specific for macrophage-tropic HIV and appears to be the result of down-regulation of CCR5, the fusion cofactor. The examiner also found Allaway et al. teach various methods to measure CCR5, including in assays measuring the effects of inhibiting fusion of HIV-1 to $CD4^+$ T cells and infection of the cells.

Applicants contend the combined references only provided an impetus to further explore how to obtain efficient induction of HIV resistance since besides Kwon fails to provide data supporting the suggestion linking down-regulation of CCR5 expression as a result of contacting T cells with anti-CD3 and anti-CD28 antibodies immobilized on beads. Furthermore, applicant contends that the state of art at the time this application is filed is not clear as to the effects using anti-CD3 and anti-CD28 antibodies on HIV infection. Figure 2 B and C of Roederer, M., Feb. 1997 (currently submitted) show that stimulation using immobilized anti-CD3/28 increases HIV replication from memory CD4 cells. Spina, C. A. Feb. 1997 (currently submitted) showed soluble anti-CD3/CD28 antibodies increased HIV replication from cultures of human CD4 memory cells. Creson, 1999 (previously submitted), teaches using immobilized anti-CD3/CD28 antibodies on plastic increases HIV production from macrophage (CCR5) tropic HIV. These references provided evidence showing that it would not have been obvious to one of ordinary skills in the art at the time this application was filed that anti-CD3 and anti-CD 28 antibodies must be immobilized on cell-sized bead to induce HIV resistance or such HIV resistance is attributed to the down-relation of CCR5 expression. One can only appreciated the very different effects of using immobilized anti-CD 3 and anti-CD28 antibodies on HIV infection and linking it to down-regulation of CCR5 after significant experimentation and study.

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144.

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather contends that the prior art does not provide sufficient suggestion or motivation to combine the teachings to arrive at combining the prior art in order to appreciated the very different effects of using immobilized anti-CD3 and anti-CD28 antibodies on HIV infection and linking it to down-regulation of CCR5 only after significant experimentation and study and addresses the teachings of the references individually and not their teachings individually or in combination.

As pointed out previously,
June et al. teach and claim a method comprising activating a population of human T cell to proliferate by contacting the cells ex vivo and in vivo with an anti-human CD3 antibodies and anti-human CD28 antibodies (e.g., see pages 5-7and 10-15 and Examples 7-9), including immobilized antibodies (e.g., see page 11, paragraph 3 and Examples 7-9 on pages 34-35) as well as the applicability of such ex vivo and in vivo methods for patients with HIV (e.g., see page 2, paragraph 3; pages 21-24 on pages 34-35) (see entire document, including Summary of the Invention and Detailed Description of the Invention).

While June et al. clearly teaches the combination of anti-CD3 antibodies and anti-CD28 antibodies for stimulating T cells as well as applicability of immobilized antibodies,
Chang et al. and Levine et al. provide a more explicit teaching of beads comprising multiple antibody specificities, including anti-CD3 antibodies and anti-CD28 antibodies.

In contrast to applicant's arguments in conjunction with Roederer, Spina and Creson that using immobilized anti-CD 3 and anti-CD28 antibodies on HIV infection and linking it to down-regulation of CCR5 only after significant experimentation and study;
Kwon et al. clearly teach that the ligation of T cells with anti-CD3 antibodies and anti-CD28 antibodies induce an HIV virus resistant state, which appears to be specific for macrophage-tropic HIV and appears to be the result of down-regulation of CCR5, the fusion cofactor (see entire document, particularly column 28, paragraph 1).

While Roederer and Spina provide some teachings concerning memory T cells,
the claims nor the prior art are limited to memory T cells.

Also, note that the Discussion of Roederer notes that the importance of interpretation of data from viral replications with cultured PBMC since the proportions of various subsets in cultures is uncontrolled and usually unknown (see page 1562, column 1, paragraph 1);
that the data presented extend the demonstration that naïve T cells are intrinsically resistant to HIV (E.g., see page 1562, column 2, paragraph 1); and
That the data presented provides for a mechanism for the observation that CD3/CD28-sitjulated ex vivo expansion of CD4 T cell from HIV-infected adults leads to eradiation of virus from cultures (e.g., see page 1563, column 1, paragraph 1).

Applicant's assertions appear to be drawn to limitations not claimed and the teachings of Roederer relied upon applicant are consistent with the prior art teachings of Kwon et al.

Also, the teachings of Creson relied upon applicant are consistent with the prior art teachings of Kwon et al. by indicating that their results confirm the observations of Levine et al. that stimulation of CD4 T cells with anti-CD3/anti-CD28 co-immobilized on magnetic beads renders the cells resistant to infection by M-tropic strains of HIV-1 (e.g., see Abstract).

Applicant's assertions that the Creson teaches using immobilized anti-CD3/CD28 antibodies on plastic increases HIV production from macrophage (CCR5) tropic HIV relies upon different culture conditions (see entire document). For example, if the beads were removed after initial stimulation, p24 production increase over time and produced a result intermediate to the other forms of stimulation (e.g., see Abstract).

However, Creson teach that resistance to infection correlated with downregulation of CCR5 expression at the T cell surface (e.g., see Abstract), which is consistent with the prior art teachings of Kwon et al.

As to the ligation of T cells with anti-CD3 antibodies and anti-CD28 antibodies for the induction of an HIV virus resistant state, which appears to be specific for macrophage-tropic HIV and appears to be the result of down-regulation of CCR5, the fusion cofactor,
such culture conditions are result effective variables

It is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804, 809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989) (determination of suitable dosage amounts in diuretic compositions considered a matter of routine experimentation and therefore obvious).

Given the clear teachings of the prior art to combine anti-CD28 and anti-CD3 stimulation to T cells in order to induce a HIV virus resistant state, which appeared to be specific for macrophage-tropic HIV and appeared to be the result of down-regulation of CCR5,
one of ordinary skill in the art at the time the invention was made would have been motivated to co-immobilize anti-CD28 and anti-CD3 antibodies on the same solid phase such as microbeads to stimulate T cells of interest, as taught by the prior art references.

Also, as noted previously, Allaway et al. teach various methods to measure CCR5, including in assays measuring the effects of inhibiting fusion of HIV-1 to $CD4^+$ T cells and infection of the cells (see entire document, including Summary of the Invention).

One cannot show non-obviousness by merely asserting that the references do not provide the sufficient elements of obviousness or by attacking references individually where the rejections are based on a combination of references. In re Young, 150 USPQ 725 (CCPA 1968).

The rationale to support a conclusion that the claims would have been obvious is that all the claimed elements of costimulating T cells with anti-CD28 and anti-CD3 antibodies to induce a HIV resistant state associated with downregulation of CCR5 were known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods of co-immobilizing anti-CD28 and anti-CD3 antibodies to stimulate T cells of interest and monitoring / analyzing CCR5 levels with no change in their respective functions and the combination would have yielded nothing more than predictable results of costimulating T cells to induce a HIV resistant state and monitoring/analyzing CCR5 levels associated with HIV resistance.

The rationale to support a conclusion that the claims would have been obvious is that a method of costimulating T cells with anti-CD28 and anti-CD3 antibodies to induce a HIV resistant state associated with downregulation of CCR5 was made part of ordinary capabilities of one skilled in the art based upon the teachings of the prior art. One of ordinary skill in the art would have been capable of applying the known means of monitoring CCR5 levels in order to monitor/analyze costimulated T cells for HIV resistance and would have been predictable to one of ordinary skill in the art at the time the invention was made.

The rationale to support a conclusion that the claims would have been obvious is that a particular known techniques of costimulating T cells with anti-CD28 and anti-CD3 antibodies (e.g., co-immobilizing anti-CD28 and anti-CD3 antibodies) to induce a HIV resistant state associated with downregulation of CCR5 and monitoring/analyzing CCR5 accordingly to do so were recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying these known techniques to costimulation of T cells to achieve a desired effect(s) that were ready for improvement and the results would have been predictable to one of ordinary skill in the art.

The rationale to support a conclusion that the claim would have been obvious is that a person of ordinary skill has good reason to pursue the known options costimulating (e.g., co-immobilizing anti-CD28 and anti-CD3 antibodies) T cells to induce a HIV resistant state and monitoring CCR5 as a means to monitor/analyze said resistance within his or her technical grasp. This leads to the anticipated success of costimulating T cells (e.g., co-immobilizing anti-CD28 and anti-CD3 antibodies) in order to induce a HIV resistant state associated with downregulation of CCR5 in T cells and monitoring the level of CCR5 accordingly. It is likely the product not of innovation but of ordinary skill and common sense.

Since co-stimulating T cells anti-CD28 and anti-CD3 antibodies to induce a HIV resistant state associated with downregulation of CCR5 would have been predictable at the time of the invention, there would have been reasonable expectation of successful development methods to do so and measuring the level of CCR5 accordingly. The prior art had recognized the advantages of co-stimulating T cells anti-CD28 and anti-CD3 antibodies to accomplish the goal of inducing a HIV resistant state. The claims were obvious because it would have been obvious to try the co-stimulating T cells anti-CD28 and anti-CD3 antibodies to accomplish the goal of inducing a HIV resistant state and measuring the downregulation of CCR5 as a means to monitor/analyze the effects of costimulation and HIV resistance with a reasonable expectation of success.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdiqital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to treat inflammatory bowel disease with fibronectin segments/fragments,
incorporating known immunoglobulins and fragments thereof such as IgG1 to increase half-life and toxin moieties as effector molecules into chimeric molecules comprising fibronectin segments/fragments would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing therapeutic molecules with improved half-life and desirable functions.

The following is reiterated for applicant's convenience.

June et al. teach and claim a method comprising activating a population of human T cell to proliferate by contacting the cells ex vivo and in vivo with an anti-human CD3 antibodies and anti-human CD28 antibodies (e.g., see pages 5-7and 10-15 and Examples 7-9), including immobilized antibodies (e.g., see page 11, paragraph 3 and Examples 7-9 on pages 34-35) as well as the applicability of such ex vivo and in vivo methods for patients with HIV (e.g., see page 2, paragraph 3; pages 21-24 on pages 34-35) (see entire document, including Summary of the Invention and Detailed Description of the Invention).

While June et al. clearly teaches the combination of anti-CD3 antibodies and anti-CD28 antibodies for stimulating T cells as well as applicability of immobilized antibodies,
Chang et al. and Levine et al. provide a more explicit teaching of beads comprising multiple antibody specificities, including anti-CD3 antibodies and anti-CD28 antibodies.

As previously noted, Chang teaches and claims a method of increasing the activation or proliferation of T cells comprising contacting T cells with a microbead coupled with a plurality of binding molecules specific for an antigen on a human T cell (see entire document).
Chang teaches that an embodiment of the invention includes using microbeads that comprise a binding molecule that is an antibody to CD3 paired with another binding molecule that is specific for T cells, including an antibody to CD28 (see entire document, especially claims 1-2 and columns 11-12).
Chang et al. teach several methods for immobilizing antibodies on solid phase surfaces that are beads, including direct immobilization via a covalent modification (see especially columns 7-8), consistent with the claimed methods.

In response to previous arguments by applicant,
given the teachings of Chang that the same product used by June et al. in vitro could also be used in vivo, the ordinary artisan would have had a reasonable expectation that the method of June et al. could also be practiced in vivo. In view of the teachings of June et al. of the beneficial effect on T cell numbers when T cells are contacted with beads on which anti-CD3 and anti-CD28 have been co-immobilized, the ordinary artisan would have been motivated to administer the beads in vivo; particularly since an in vivo method would obviate potential sources of

secondary infection due to ex vivo expansion of the T cells and would reduce the risk of exposure of health care workers to HIV infected cells.

In addition to the teachings of June et al. and Chang et al.,
Levine et al. teach the applicability of beads coated with both anti-CD3 antibodies and anti-CD28 antibodies in the stimulation of T cells of interest (see entire document, including Long-term Cell Cultures on page 893, column 1).

June et al. in view of Chang et al. and Levine et al. differ from the claims not measuring the level of CCR5 expression in T cells contacted with anti-CD3 antibodies and anti-CD28 antibodies.

As pointed out previously, Kwon et al. teach that the ligation of T cells with anti-CD3 antibodies and anti-CD28 antibodies induce an HIV virus resistant state, which appears to be specific for macrophage-tropic HIV and appears to be the result of down-regulation of CCR5, the fusion cofactor (see entire document, particularly column 28, paragraph 1).

As noted previously, Allaway et al. teach various methods to measure CCR5, including in assays measuring the effects of inhibiting fusion of HIV-1 to $CD4^+$ T cells and infection of the cells (see entire document, including Summary of the Invention).

Given the teachings of the beneficial effects of contacting T cells with anti-CD3 and anti-CD28 antibodies to increase HIV resistance and that this beneficial effect was a result of down-regulation of CCR5 as taught by the prior art, one of ordinary skill in the art at the time the invention was made would have been motivated to monitor the expression of CCR5 expression to monitor the effect of combining anti-CD3 and anti-CD28 antibodies on T cell populations on HIV expression. In addition, the prior art provides for the co-immobilization of anti-CD3 and anti-CD28 on the same bead as a means of stimulating T cells. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

4. No claim allowed.

5. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/
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